Predicting biochemical recurrence after radical prostatectomy: The role of prognostic grade group and index tumor nodule

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ABSTRACT

The aim of the current study was to test whether the grade group assessed in the index tumor nodule predicts biochemical recurrence after surgery. The study cohort series included 144 consecutive patients treated by laparoscopic radical prostatectomy. The following parameters were evaluated in each case: type of radical prostatectomy (with/without lymphadenectomy), pT and pN status, histologic type of prostate carcinoma (acinar vs. mixed histology), surgical margin resection status, perineural invasion, lymphovascular invasion, biochemical recurrence status, presence of tertiary Gleason 5 pattern, and grade group that was assessed, both, in overall prostate cancer and in index (dominant) tumor nodule. Twenty patients (13.9%) experienced postoperative biochemical recurrence at a mean followup time of 12.2 months. The univariate survival analysis selected type of radical prostatectomy, histological subtype, lymphovascular invasion, AJCC pT and pN classification, tertiary Gleason 5 pattern, preoperative PSA level, and the grade group assessed in both the overall prostate and index tumor nodule as significant for biochemical recurrence-free survival. Type of radical prostatectomy (P=.020), histological subtype (P=.002), lymphovascular invasion (P=.023), tertiary Gleason pattern 5 (P=.016), and grade group classification in index tumor nodule ($P\leq$.0001) were selected as independent predictors of biochemical recurrence-free survival. In conclusion, our results validate grade group in the index tumor nodule as an independent predictor of biochemical recurrence-free survival; thus, emphasizing the value of reporting grade group in index tumor nodule. The main limitation of our study is the relatively low number of cases in the current series, suggesting the need of large confirmatory studies.

Keywords: Prostate cancer; radical prostatectomy; index tumor; index nodule; grade groups; biochemical recurrence

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1. INTRODUCTION

Gleason score is one of the most powerful pathological predictive factors of biochemical recurrence after radical prostatectomy [1-12]. To further improve Gleason score prognostic value in this setting, the WHO (2016) has incorporated the "grade group" system based on an earlier proposal by Jonathan I. Epstein and co-workers [13-34]. The "grade group" system has been validated in several large-scale studies, demonstrating increased predictive accuracy of both biochemical recurrence and mortality following radical prostatectomy [7-17, 19]. Conversely, most prostate cancers present as multifocal disease with two or more tumor nodules in the prostate gland [1-3, 34, 37]. Histologically, different tumor nodules in the same prostatectomy specimen often show different Gleason scores and, therefore, different grade groups [2, 3, 5, 7, 11, 12, 21, 23, 24, 29]. To circumvent this issue, McNeal et al introduced the concept of "dominant/index tumor nodule" referring to a tumor nodule likely to harbor the most aggressive biological behavior among the multifocal tumor nodules within the prostate, which may dictate the overall biological behavior of the disease [25]. This controversial concept reflects the lack of consensus on the pathological parameters that defined the index tumor nodule in radical prostatectomy specimens [2, 3, 7, 12, 15, 18, 20, 21, 23, 26, 27, 30, 32, 35-41]. Current available data on the pathological features of index tumor nodule in multifocal prostate cancer is, however, quite limited. Likewise, according to most authorities, at present, index tumor nodule refers to the tumor nodule of the largest size in a multifocal disease [25-27, 30].

The concept of index tumor nodule has recently received considerable interest since it might also predict biochemical recurrence [1, 4, 6, 10, 20]. Reported experience also suggests that the index tumor nodule is not only the largest but also holds the highest Gleason score and is often the stage-determining tumor, as suggested by Karavitakis et al [26]. However, it is useful to note

that the index tumor nodule might not include the highest Gleason score, extraprostatic extension status, or the highest tumor volume in about 10% of cases [30]. In clinical terms, this concept is also appealing. Since the characteristics of the index tumor nodule may dictate the biologic behavior and the lethality of the tumor, a selective destruction of this lesion by means of focal therapy could potentially prevent or delay cancer progression [28, 31]. An additional advantage of the concept is the capability, by multiparametric MRI, to accurately identify the index tumor nodule in most patients, reportedly 9 in 10 patients, allowing targeting biopsies to identify more aggressive prostate cancer when multiparametric MRI guided [32, 36, 41-43]. Therefore, the potential of classifying prostate cancer in risk categories based in the index tumor nodule and its associated grade group category holds great promise and deserves to be substantiated.

We hypothesized that grade group assessment in the index tumor nodule may better predict features of aggressive prostate cancer as compared with grade group assessed in the overall prostate. To answer this question, we have compared grade group in the index tumor lesion and in the overall prostate in a sequential cohort series of 144 laparoscopic radical prostatectomies in which followup was available. Other known prognostic parameters of prostate cancer also entered the study for comparison purposes or to assess the performance status of the current study.

2. MATERIAL AND METHODS

2.1. Patient cohort

The study is based on 144 consecutive laparoscopic radical prostatectomies performed by two urologists experienced (>14 years) in laparoscopic prostatectomy and evaluated at our hospital between August 2012 and April 2016. None of the patients had androgen deprivation treatment or preoperative radiotherapy. Radical prostatectomy specimens were inked, sliced serially (at 3–

5mm intervals), and examined by an experienced urologic pathologist (ALB). The entire prostate was embedded for all cases. We used the 2014 modified Gleason scoring system and the grade groups [5, 7, 11-15, 19, 34]. For the purpose of the study, grade group was retrospectively assigned to some earlier cases and AJCC/pTNM adjusted to 2017 8th edition [18].

The clinicopathological variables were prospectively collected and reviewed. Information included age (years) at surgery, Gleason score and grade group at radical prostatectomy, pathological stage category, and followup data on biochemical recurrence. Other analyzed parameters including lymphovascular or perineural invasion, extraprostatic extension, seminal vesicle invasion, and surgical margin status were assessed following reported criteria [2, 3, 9, 34, 36, 41]. For the purpose of this study, the index tumor nodule (dominant nodule) was defined as the largest nodule measured linearly in mm. For the assessment, we measured the index nodule linearly in all related glass slides, and then the larger one was selected as the measurement of the index nodule lesion for that particular case. The vertical growth was not taken in consideration for the purpose of the study. The frequently observed infiltrative foci at the edge of the index nodule lesion, was included in the final measurement, even if it was discontinuous, if the pathologist was confident to consider related to it. Figure 1 A dedicated genitourinary pathologist signed-out all specimens.

Patients were followed after surgery, according to the accepted guidelines, with PSA levels being typically checked at 3-month intervals for the first year and every 6 months for the subsequent 2 years. Biochemical recurrence following surgery was considered as PSA measurement >0.2 ng/mL [34]. The current project received the Institutional Review Board approval.

2.2. Statistical analysis

Categorical variables were presented as frequencies and percentages, and were compared using the *t* test or chi-square test when appropriated. Continuous variables were expressed as mean ± standard deviation. The Kolmogorov–Smirnov test was used for normality analysis and nonparametric tests were used accordingly. The association between continuous variables and study variables was compared through the Mann–Whitney/Kruskal–Wallis.

Survival curves (time to biochemical recurrence) were calculated using the product-limit method (Kaplan–Meier curves). Kaplan–Meier curves were constructed in order to demonstrate the probability of remaining free of biochemical recurrence as a function of time after radical prostatectomy. Statistically significant survival differences between groups were tested by applying a Log-rank test (Mantel–Cox).

Cox proportional hazards regression analysis was performed to test the statistical independence with associated 95% confidence intervals between clinical preoperative and pathologic postoperative variables. For each variable analyzed, the assumption that no predictive value existed was rejected if $P>.05$. Statistical analysis was performed with all statistical analyses were performed with standard statistical software SPSS 17.0 version (SPSS, Inc., IL, USA).

3. RESULTS

Characteristics of 144 patients in the study are summarized in Table 1. The mean age at surgery was 61.38 years. The median preoperative PSA was 8.11 ng/mL. The patients were treated with radical prostatectomy alone (51%) or radical prostatectomy with extended lymph node dissection (49%). The mean followup for the entire cohort of patients was 27.9 months (12.8–60.7). During followup, 20 patients (13.9%) experienced biochemical recurrence. The mean age at time of biochemical recurrence was 63 years (50.5–74.6) with a median time to recurrence of 12.2

months (1.9–30.3). Mean index tumor nodule linear extension was about 19.3 mm (range, 4–44 mm).

Localized disease was seen in 57% of patients and locally advanced disease was observed in 43%. Lymph node metastasis was seen in 11% of the 71 patients who underwent lymphadenectomy. Pure acinar adenocarcinoma was the most frequent histologic subtype (72%) but mixed acinar/non-acinar histology was seen in 28% of patients. Twenty percent of patients had positive resection margins. Perineural invasion and lymphovascular invasion were seen in 89% and 5%, respectively. Tertiary Gleason pattern 5 (TGP5) was present in 2.1% of the cases.

Preoperative PSA, treatment type, grade group classification both in the overall specimen and in the index tumor nodule, pT and pN status, histologic subtype, lymphovascular invasion, and TGP5 were all associated with biochemical recurrence in our cohort series (Table 2).

The most common grade group was 2 (GG2), both in the index tumor nodule (71%) and in overall prostate cancer (80%). In general, the higher grade group was seen in index tumor nodule, not in overall prostate cancer: GG3 32% vs. 24%, GG4 8% vs. 6%, and GG5 3% vs. <1% ($P<0.001$). Table 3

Grade groups in overall prostate cancer were associated with grade group in index tumor, treatment type, pT and pN status, histological subtype, lymphovascular invasion, and the presence of TGP5 (Table 3).

The univariate survival analysis, selected treatment type, histological subtype, lymphovascular invasion, pT and pN status, the presence of TGP5, preoperative PSA, and grade groups determined in both the overall prostate cancer and the index tumor nodule were all associated with biochemical recurrence-free survival (Table 4; Figure 2). Cox multivariate analysis selected type of radical prostatectomy, histological subtype, lymphovascular invasion,

TGP5, and grade group assessed in the index tumor nodule as independent predictors of biochemical recurrence-free survival in our series (Table 4).

4. DISCUSSION

Different candidate pathologic parameters were evaluated in an attempt to predict biochemical recurrence following radical prostatectomy, Gleason score being considered one of the most powerful predictive factors [1-41]. To improve grading of prostate carcinoma and to lower the current limitations of the Gleason score, it has been internationally recommended to implement Epstein's prognostic grade grouping system, recently endorsed by the WHO classification of genitourinary cancer under the designation of grade groups [14, 34]. Prognostic grade groups have been validated as predictive of biochemical recurrence, response to therapy, and cancer-related mortality in several large-scale studies [7,14-17].

Contemporary defined index tumor nodule (larger prostate cancer nodule in multifocal disease) which frequently harbors the highest Gleason score has also been shown to be predictive of biochemical recurrence. It is, therefore, considered an important prognostic parameter in prostate cancer after radical prostatectomy [26-28, 30]. In fact, recent studies suggest that index tumor nodule can be identified in about 90% of radical prostatectomy samples and may be identified in 90% patients using multiparametric MRI and targeted biopsies [26-28, 30, 41-43].

Our study showed that identification of the grade group system in the index tumor nodule is feasible and of potential clinical relevance. In fact, the grade group was selected as a predictor of biochemical recurrence when assessed in overall prostate cancer, but turned out to be an independent predictor of biochemical recurrence-free survival when assessed in the index tumor nodule; an original contribution of our study emphasizing the effect of adding grade group to index tumor nodule since both parameters are considered powerful predictors of aggressive

features after radical prostatectomy. Hypothetically, the observed good correlation and adding effects of grade group in index tumor nodule, could give support to emerging clinically oriented proposals of using multiparametric MRI to summarize the aggressive features based on index tumor nodule features. This could lower unnecessary surgical procedures or provide a rational for focal therapy applications within the frame of grade group assessed in index tumor. Along this line, Radtke et al was able to identify over 90% of index tumor nodules in a series of radical prostatectomies aiming towards focal therapy and concluded that multiparametric MRI could identify 92% of index lesions [32]. Kasivisvanatha et al was able to identify higher grade tumors as compared to standard-biopsy, a fact that might be related a higher detection of index tumor lesions because of MRI guiding targets. In support of this is our finding of higher grade group categories in index tumor nodule, as compared with all prostate. [43]

It is also important to bear in mind that our study included patients treated by laparoscopic radical prostatectomy only; these results might need to be validated for other surgical modalities.

Our study also included the analysis of other known prognostic parameters in radical prostatectomy treated patients. Of relevance, as shown by the multivariate analysis, are type of radical prostatectomy (with/without lymphadenectomy), histological subtype (acinar vs. mixed), lymphovascular invasion, and the presence of TGP5. They were all independent predictors of biochemical recurrence-free survival. These results are not surprising and are in line with the current knowledge [1-41]. They most probably reflect an adequate therapy selection based on the current guidelines and validated nomograms. Therefore, our observation that the type of radical prostatectomy is an important predictor of biochemical recurrence is in agreement with the expected results since radical prostatectomy with extended lymphadenectomy is indicated in patients with more aggressive clinicopathologic features.

Another relevant observation in our series is that phenotypically mixed forms of prostate cancer beyond pure acinar predicts independently biochemical recurrence-free survival [7, 13, 21, 33-35, 38-41]. This result concurs with previous observations regarding variants or morphologies associated with prostate cancer: that is ductal/intraductal/large cribriform morphologies, among others, are known to be associated with poor prognosis [7, 13, 21, 33-35, 38-41]. Lymphovascular invasion is also known as an aggressive parameter in prostate cancer. A recently reported retrospective analysis of pathological and clinical data from 14,528 consecutive patients concluded that analysis of lymphatic invasion provides comparable prognostic information than lymph node analysis. Therefore, suggesting that even minimal involvement of the lymphatic system has a decisive prognostic impact in prostate cancer [9].

The presence of a TGP5, in patients with GS 7, was also associated with biochemical recurrence in our series and is in line with previous reports supporting higher grade elements, such as tertiary Gleason pattern in radical prostatectomy, have an adverse influence on prognosis [40]. Finally, our results agree with recent studies showing an excellent correlation between grade groups and different aggressive features in prostate cancer [7-19]. We also add further validation to the use of the prognostic grade group system in radical prostatectomy not only in large academic centers, but also in a comprehensive cancer center. Our study also found an independent predictive value of the grade group enriched index tumor nodule, a finding not previously reported and of relevance currently because of the increasing use of imaging methods such as multiparametric MRI. The limitations of our study include a limited followup of 28 months and a relative low number of cases (n=144); therefore, our results should be interpreted with the necessary caution.

In conclusion, to our knowledge, this is the first study evaluating prostate cancer prognostic grade group in the index tumor nodule as predictor of biochemical recurrence after laparoscopic radical prostatectomy. Our results support reporting grade group system in the index tumor nodule since it better predicts biochemical recurrence than the grade group system assessed in the overall prostate cancer.

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Table 1- Clinical and pathologic features of 144 patients who underwent laparoscopic radical prostatectomy.

Table 2 – Parameters associated with biochemical recurrence in a cohort series of 144 patients treated by laparoscopic radical prostatectomy.

Table 3- Overall prostate grade-group compared to clinico-pathologic variables including the grade-group assessment in the index tumor.

Table 4 - Univariate and multivariate analysis including separate models for grade group evaluation in the overall prostate (model 1) and index tumor lesion (model 2).

Table 1. Clinical and pathologic features of 144 patients who underwent laparoscopic radical prostatectomy

Mean age, year ±SD (range)	61.38±5.58 (47–75)	
Mean preoperative PSA ng/ ml (range)	8.11±4.91 (1–23)	
	N=144	**%**
Treatment type		
Radical prostatectomy	73	50.7
Radical prostatectomy with lymphadenectomy	71	49.3
Prognostic grade group (Gleason score) overall prostate		
Grade group 1 (Gleason score ≤6)	19	13.2
Grade group 2 (Gleason score 3+4=7)	80	55.6
Grade group 3 (Gleason score 4+3=7)	35	24.3
Grade group 4 (Gleason score 4+4=8)	9	6.3
Grade group 5 (Gleason score 9–10)	1	0.7
Prognostic grade group (Gleason score) (index tumor)		
Grade group 1 (Gleason score ≤6)	11	7.6
Grade group 2 (Gleason score 3+4=7)	71	49.3
Grade group 3 (Gleason score 4+3=7)	46	31.9
Grade group 4 (Gleason score 8)	12	8.3
Grade group 5 (Gleason scores 9–10)	4	2.8
pT status (AJCC 2017)		
pT2	82	56.9
pT3a	44	30.6
pT3b	18	12.5
pN status		
N0	63	43.8
N1	8	5.6
Nx	73	50.7

Histological subtype		
Acinar	104	72.2
Mixed	40	27.8
Surgical resection margin status		
R0	115	79.9
R1	29	20.1
Perineural invasion		
No	16	11.1
Yes	128	88.9
Lymphovascular invasion		
No	137	95.1
Yes	7	4.9
Biochemical recurrence		
No	124	86.1
Yes	20	13.9
TPG5		
No	141	97.9
Yes	3	2.1

AJCC, American Joint Committee on Cancer; PSA, serum prostate specific antigen; SD, standard deviation of the mean; TPG5, tertiary pattern of Gleason 5

Table 2. Parameters associated with biochemical recurrence in a cohort series of 144 patients treated by laparoscopic radical prostatectomy

Value	Biochemical Recurrence		*P* Value*
	No	Yes	
Age. n (mean±SD)	124 (61.37±5.56)	20 (61.40±5.86)	0.983**
PSA. n (mean±SD)	120 (7.74±4.67)	20 (10.31±5.82)	**0.030****
Treatment type			**0.001**
Radical prostatectomy	70 (56.5%)	3 (15.0%)	
Radical prostatectomy with lymphadenectomy	54 (43.5%)	17 (85.0%)	
Grade group (Gleason score), overall prostate			**<0.001**
Grade group 1 (Gleason score ≤6)	19 (15.3%)	0 (0.0%)	
Grade group 2 (Gleason score 3+4=7)	75 (60.5%)	5 (25.0%)	
Grade group 3 (Gleason score 4+3=7)	24 (19.4%)	11 (55.0%)	
Grade group 4 (Gleason score 4+4=8)	6 (4.8%)	3 (15.0%)	
Grade group 5 (Gleason score 9–10)	0 (0.0%)	1 (5.0%)	
Grade group (Gleason score), index tumor			**<0.001**
Grade group 1 (Gleason score ≤6)	11 (8.9%)	0 (0.0%)	
Grade group 2 (Gleason score 3+4=7)	69 (55.6%)	2 (10.0%)	
Grade group 3 (Gleason score 4+3=7)	37 (29.8%)	9 (45.0%)	
Grade group 4 (Gleason score 8)	7 (5.6%)	5 (25.0%)	
Grade group 5 (Gleason scores 9–10)	0 (0.0%)	4 (20.0%)	
pT status (AJCC 2017)			**0.009**
pT2	76 (61.3%)	6 (30.0%)	
pT3a	36 (29.0%)	8 (40.0%)	
pT3b	12 (9.7%)	6 (30.0%)	
pN status			**0.005**
N0	50 (40.3%)	13 (65.0%)	
N1	5 (4.0%)	3 (15.0%)	
Nx	69 (55.6%)	4 (20.0%)	

Histological subtype			**0.003**
Acinar	95 (76.6%)	9 (45.0%)	
Mixed	29 (23.4%)	11 (55.0%)	
Surgical resection margin status			0.236
R0	101 (81.5%)	14 (70.0%)	
R1	23 (18.5%)	6 (30.0%)	
Perineural invasion			0.088
No	16 (12.9%)	0 (0.0%)	
Yes	108 (87.1%)	20 (100.0%)	
Lymphovascular invasion			**0.001**
No	121 (97.6%)	16 (80.0%)	
Yes	3 (2.4%)	4 (20.0%)	
TPG5			**<0.001**
No	124 (100.0%)	17 (85.0%)	
Yes	0 (0.0%)	3 (15.0%)	

*Chi-square

**Student *t*-test

AJCC, American Joint Committee on Cancer; PSA, serum prostate specific antigen; SD, standard deviation of the mean; TPG5, tertiary pattern of Gleason 5

Table 3. Overall prostate grade-group compared to clinico-pathologic variables including the grade-group assessment in index tumor lesion.

	Overall Grade Group					***P* value***
	Group 1	**Group 2**	**Group 3**	**Group 4**	**Group 5**	
Age. n (mean±SD)	19 60.32±7.8	80 61.1±5.9	35 62.2±.56	9 61.8±5.7	1 60.0±0.0	0.667**
PSA. n (mean±SD)	17 6.5±3.6	79 7.4±4.6	34 9.9±6.3	9 8.0±3.5	1 6.0±0.0	0.097**
Treatment type						**<0.001**
Radical prostatectomy	13 (6.4%)	52 (65.0%)	6 (17.1%)	2 (22.2%)	0 (0.0%)	
Radical prostatectomy + lymphadenectomy	6 (31.6%)	28 (35.0%)	29 (82.9%)	7 (77.8%)	1 (100.0%)	
Grade group (index tumor)						**<0.001**
Grade group 1 (Gleason score ≤6)	11 (57.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
Grade group 2 (Gleason score 3+4=7)	8 (42.1%)	61 (76.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	
Grade group 3 (Gleason score 4+3=7)	0 (0.0%)	17 (2.3%)	29 (82.9%)	0 (0.0%)	0 (0.0%)	
Grade group 4 (Gleason score 8)	0 (0.0%)	2 (2.5%)	2 (5.7%)	8 (88.9%)	0 (0.0%)	
Grade group 5 (Gleason scores 9–10)	0 (0.0%)	0 (0.0%)	2 (5.7%)	1 (11.1%)	1 (100.0%)	
pT status (AJCC 2017)						**<0.001**
pT2	15 (78.9%)	55 (68.8%)	11 (31.4%)	1 (11.1%)	0 (0.0%)	
pT3a	4 (21.1%)	20 (25.0%)	13 (37.1%)	6 (66.7%)	1 (100.0%)	
pT3b	0 (0.0%)	4 (21.1%)	11 (31.4%)	2 (22.2%)	0 (0.0%)	
pN						**<0.001**
N0	7 (36.8%)	26 (32.5%)	25 (71.4%)	4 (44.4%)	1 (100.0%)	
N1	0 (0.0%)	2 (2.5%)	4 (11.4%)	2 (22.2%)	0 (0.0%)	
Nx	12 (63.2%)	52 (65.0%)	6 (17.1%)	3 (33.3%)	0 (0.0%)	
Histological subtype						**0.021**
Acinar	19 (100.0%)	58 (72.5%)	21 (60.0%)	5 (55.6%)	1 (100.0%)	
Mixed	0 (0.0%)	22 (27.5%)	14 (40.0%)	4 (44.4%)	0 (0.0%)	
Margin status						0.374
R0	15 (78.9%)	67 (83.8%)	24 (68.6%)	8 (88.9%)	1 (100.0%)	
R1	4 (21.1%)	13 (16.3%)	11 (31.4%)	1 (11.1%)	0 (0.0%)	

Perineural invasion						0.307
No	5 (26.3%)	9 (11.3%)	2 (5.7%)	0 (0.0%)	0 (0.0%)	
Yes	14 (73.7%)	71 (88.8%)	33 (94.3%)	9 (100.0%)	1 (100.0%)	
Lymphovascular invasion						**<0.001**
No	18 (94.7%)	79 (98.8%)	31 (88.6%)	9 (100.0%)	0 (0.0%)	
Yes	1 (5.3%)	1 (1.3%)	4 (11.4%)	0 (0.0%)	1 (100.0%)	
TPG5						**0.049**
No	19 (100.0%)	80 (100.0%)	32 (91.4%)	9 (100.0%)	1 (100.0%)	
Yes	0 (0.0%)	0 (0.0%)	3 (8.6%)	0 (0.0%)	0 (0.0%)	

*Chi-square

**ANOVA test

AJCC, American Joint Committee on Cancer; PSA, serum preoperative prostate specific antigen; TPG5, tertiary pattern of Gleason 5

Table 4. Univariate and multivariate analysis including separate models for grade group evaluation in the overall prostate (model 1) and index tumor lesion (model 2).

UNIVARIATE SURVIVAL ANALYSIS	***P* Value**	**HR**	**95.0% CI**	
Treatment type RP vs. RP+LND	**0.010**	5.119	1.489	17.593
Histological subtype	**0.001**	5.022	1.986	12.700
Margin status	0.208	1.852	0.710	4.835
Perineural invasion	0.307	24.20	0.053	10981.062
Lymphovascular invasion	**0.001**	5.997	1.996	18.016
AJCC classification				
pT2 vs pT3	**0.020**	3.128	1.201	8.143
pN				
N0		1.00 (Ref)		
N1	0.163	2.456	0.700	8.608
Nx	**0.045**	0.315	0.102	0.969
TPG5	**0.0001**	10.256	2.957	35.579
PSA (pre-surgery)	**0.032**	1.081	1.007	1.161
Age at diagnosis	0.863	0.993	0.918	1.074
Univariate analysis for grade group in overall prostate (model 1)				
Grade group 1	0.966	0.000		
Grade group 2		1.00 (Ref)		
Grade group 3	**0.006**	4.461	1.551	12.829
Grade group 4	**0.038**	4.731	1.101	20.363
Grade group 5	**0.004**	23.628	2.721	205.129
Univariate analysis for grade group in index tumor (model 2)				
Grade group 1	0.9623	0.000		
Grade group 2		1.00 (Ref)		

Grade group 3	**0.015**	6.671	1.451	30.671
Grade group 4	**0.002**	14.880	2.822	78.463
Grade group 5	**<0.000**	62.499	11.230	347.837
MULTIVARIATE SURVIVAL ANALYSIS				
Treatment type: RP vs. RP+LND	**0.020**	4.439	1.277	15.423
Histological subtype: Acinar vs. mixed	**0.002**	2.133	1.3262	3.431
Lymphovascular invasion	**0.023**	3.795	1.208	11.919
TPG5	**0.016**	4.819	1.358	17.102
Grade group in index tumor (model 2)				
Grade group 2		1.00 (Ref)		
Grade group 3	**0.044**	5.005	1.048	23.899
Grade group 4	**0.007**	10.858	1.966	59.953
Grade group 5	**<0.000**	40.484	6.9756	234.951

AJCC, American Joint Committee on Cancer; CI, confidence interval; HR, hazard ratio; LND, lymphadenectomy; PSA, serum prostate specific antigen; RP, radical prostatectomy; TPG5, tertiary pattern of Gleason 5

Figure 1 – Gross picture of an index tumor lession in the prostate (right) and an addition smaller tumor (left) (laparoscopic radical prostatectomy; case# 16H01051)

Figure 2 – Univariated survival analysis with Kaplan-Meier plots and log-rank analysis indicating biochemical recurrence-free survival differences of patients after laparoscopic radical prostatectomy. Cox's multivariate analysis selected these parameters as independent predictors (A, B, C, D, E). Figure E refers to the index tumour. RP: Radical Prostatectomy; RP+LN: Radical prostatectomy plus lymphadenectomy (PR+LN).Lymphovascular invasion presence (LVI+) or absent (LVI). Tertiary Gleason pattern 5 present (TG5+) or absent (TG5-). GG1 to 5: Grade-group 1 to 5.

Highlights

Type of radical prostatectomy (with or without) lymph node , histological subtype (acinar vs. mixed) of prostate adenocarcinoma, lymphovascular invasion, tertiary Gleason pattern 5, and grade group assessment in the index tumor nodule are independent predictors of biochemical recurrence-free survival after radical prostatectomy.

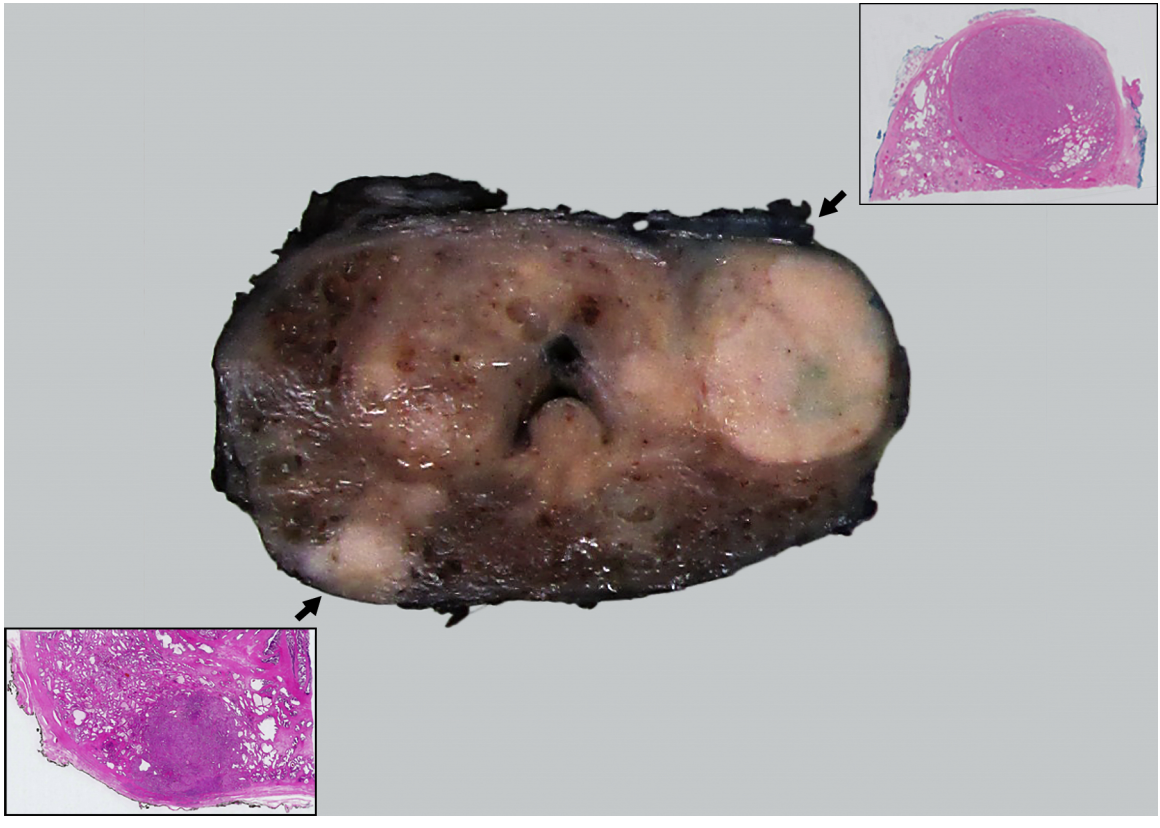
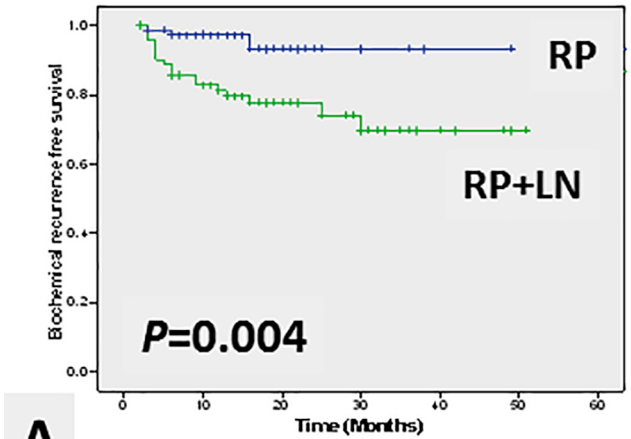
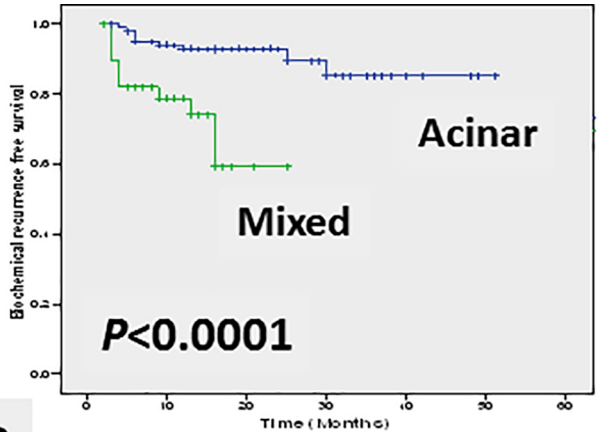


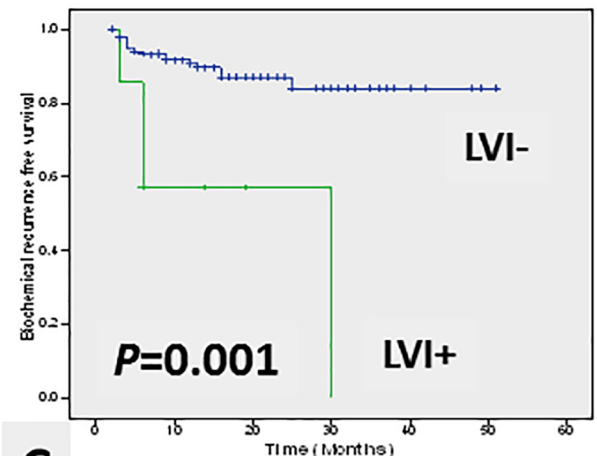
Figure 1



A



B



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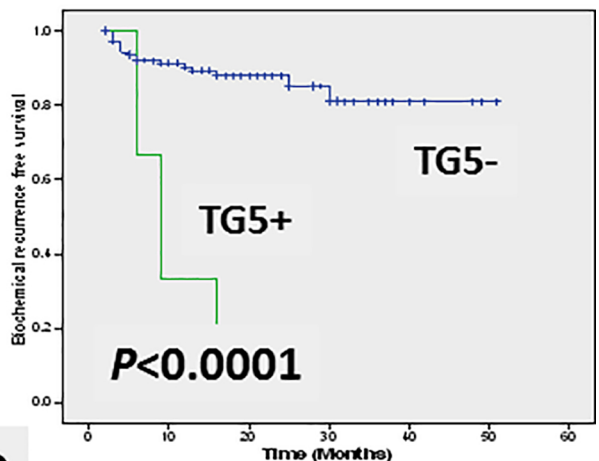

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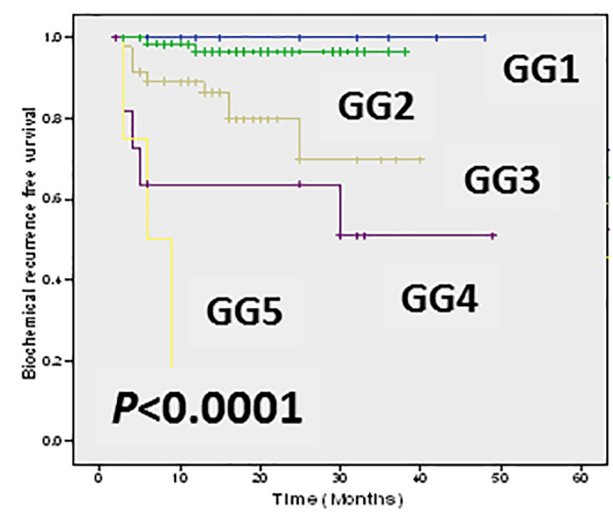

E

Figure 2